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Minireview

Donor Intervention and Organ Preservation: Where Is the Science and What Are the Obstacles?

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The organ shortage is widely acknowledged as the most critical factor hindering the full realization of success for solid organ transplantation. Innovation in the areas of donor management and organ preservation offers the most realistic hope to improve both the quality and size of the current organ supply. Although the basic science dissecting the complex processes of brain death and ischemia/reperfusion injury is replete with exciting discoveries, the clinical science investigating donor management and organ preservation is sparse in contrast. This review will survey the current landscape of trials to mitigate organ injury through interventions administered to donors *in vivo* or organs *ex vivo.* Consideration will then be given to the scientific, logistical and ethical obstacles that impede the transformation of laboratory breakthroughs into innovative treatments that simultaneously improve organ quality and supply.

Key words: Donors, graft function, injury, ischemia/reperfusion, marginal

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Introduction

It is clear that the success of solid organ transplantation has been a major contributing factor to what is becoming its primary failure – the woefully insufficient supply of organs. As results have improved, demand has increased with emergence of new transplant indications and the disappearance of contraindications. Although the life-saving nature of heart, lung, liver and small intestinal transplantation is intuitive, the survival benefit of kidney transplantation has been demonstrated (1). The demand for solid organ transplantation is also driven by improvements in quality of life improvement.

To meet the steep increase in transplant demand, the transplant community has creatively expanded the organ supply. The most successful strategy has been living donor organ donation (2). Historically limited to kidney transplantation, living donation has now embraced lung, liver, pancreas and intestinal transplantation. The number of living donors actually surpassed deceased donors for 2001, 2002 and 2003.

In deceased donor transplantation, the liver has supported the unique strategy of splitting a single organ into two grafts to transplant two recipients. However, the general approach to increase the deceased donor organ supply has been to pursue potential donors aggressively and to accept a broader range of organs for transplantation. The effort to procure more organs from more donors has been clearly articulated by three successive donation and transplantation Breakthrough Collaboratives that were launched in 2003, 2005 and 2006 (3). These initiatives, focused on setting ambitious goals for organ procurement and transplantation along with identification and dissemination of best systems and practices, have yielded rich rewards of steep increases in the annual number of deceased donors. Parallel to the expansion of the donor pool, there has been an undeniable change in its profile, with a steady increase in donor age and medical co-morbidities (2). Within the last decade, new terminology, the 'marginal' or the 'expanded criteria' donor, connoting reduced organ quality and transplant outcomes, has emerged and is now standard in the transplantation vocabulary. Theoretically, innovation in donor management and organ preservation could improve graft function and transplant outcomes, facilitating further expansion of donor horizons without decrement in outcomes. This article aims to review the basic principles underlying brain death and ischemia reperfusion injury as a springboard to examine today's investigative milieu of clinical trials in donor intervention and organ preservation.

Principles of Donor Management

It is well known that brain death is a physiologic, cellular and molecular catastrophe (4,5). Focus of clinical donor management centers on achieving and maintaining normal hemodynamics, cardiac output, volume status, oxygenation, ventilation, electrolyte balance, acid base status, coagulation parameters and normothermia. Restoration of a favorable hemodynamic, endocrine and metabolic milieu to optimize organ viability and function in anticipation of procurement, preservation and transplantation

often requires invasive monitoring with central venous or pulmonary artery catheters, transthoracic or transesophageal echocardiography, and appropriate use of vasoactive and inotropic agents. Recent guidelines advocate for the use of a standardized hormonal resuscitation package consisting of methylprednisolone or low-dose hydrocortisone, triiodothyronine and arginine vasopressin along with insulin to correct endocrine insufficiency (6,7). There have been multiple publications reporting that an aggressive donor management policy improves organ quality and increases number of organs transplanted per donor (8–11).

Recent Trials in Donor Intervention

A thorough search of the literature identified three recently completed donor intervention trials aimed at optimizing transplant organ function. First, there is a prospective randomized trial of methylprednisolone to improve liver transplant function (12). Methylprednisolone treatment comprised of an intravenous bolus of 250 mg when consent for organ donation is secured followed by a continuous infusion at 100 mg/hour until organ recovery. One hundred deceased donors were prospectively randomized between 2003 and 2006 in a single-center study. Methylprednisolone reduced serum levels of many inflammatory cytokines and liver expression of adhesion, migration, apoptosis and lymphocyte infiltration genes. These molecular changes occurred in conjunction with amelioration of ischemia/reperfusion injury and lower acute rejection rates after liver transplantation.

The second published donor intervention trial is dopamine administration to improve kidney transplant outcomes (13). Dopamine treatment comprised of a continuous infusion (4 μg/kg/min) initiated after informed consent for study inclusion and continued until crossclamp. The study included 264 hemodynamically stable brain dead donors with preserved renal function and 487 subsequent renal transplants between March 2004 and August 2007. Dopamine was infused for a median of 344 minutes and decreased the need for multiple dialysis treatments after transplantation, the endpoint that was strongly correlated with 3-year allograft failure (hazard ratio [HR] 3.61; 95% CI 2.39–5.45; $p < 0.001$). In addition to donor dopamine infusion (odds ratio [OR] 0.54; 95% CI 0.35–0.83; $p = 0.005$), three other factors, cold ischemia time (OR 1.07; 95% CI 1.02–1.11 per hour; $p = 0.001$), donor age (OR 1.03; 95% CI 1.01–1.05 per year; $p = 0.001$) and recipient body weight (OR 1.02; 95% CI 1.01–1.04 per kg; $p = 0.009$) emerged as independent risk factors for multiple dialysis treatments. The authors argued that dopamine improved early posttransplant renal function not through circulatory stabilization as this was an inclusion criterion but rather by protecting endothelial cells from oxidative stress thereby mitigating the injurious effect of cold storage.

The third and, perhaps, the most novel published donor intervention trial is a pilot study to explore the feasibility of using a hemoadsorption device to remove cytokines (14). Eight brain dead subjects ruled out for organ donation were treated with hemoadsorption for 4 h with modest reduction in cytokine plasma concentrations and without adverse consequences. The authors argue that these results merit larger, controlled trials to not only further delineate safety but also explore clinical efficacy.

A thorough search of the www.clinicaltrials.gov website reveals a list of only six ongoing donor intervention trials (Table 1). A dominant theme is ischemic preconditioning (15,16), the imposition of brief periods of ischemia to either the organ of interest (local) or another organ (remote) with the goal of inducing cell survival and protection pathways to increase resistance to a subsequent ischemic insult. Completed liver transplant trials have shown, at best, reduction of peak aminotransferases, cell death markers and/or inflammatory infiltrates without improvement in recipient or graft survival (15–17). One ongoing trial (NCT00718575; Table 1) augments local ischemic preconditioning with a mesenteric infusion of glucose and insulin immediately prior to cold flush. A second ongoing trial (NCT00975702; Table 1) imposes remote ischemic preconditioning by vascular occlusion of both lower extremities with the aim to study the impact on kidney, liver and pancreas transplant function. Of the remaining four ongoing studies, minimal information is provided on a trial of comparing oral versus intravenous administration of thyroid hormone to deceased donors initiated over five years ago (NCT00238030; Table 1). An Italian trial is designed to compare the standard ventilatory approach based on high tidal volume and low positive end expiratory pressure (PEEP) to a 'protective' ventilatory approach characterized by low tidal volume and PEEP on the number of lungs that meet criteria for transplantation and the number that are actually transplanted (NCT 00260676; Table 1). A French study tests the efficacy of intravenous N-acetyl-cysteine administration to organ donors before and after cerebral angiography in the prevention of kidney delayed graft function after transplantation (NCT998972; Table 1). The final ongoing study (NCT00987714; Table 1) compares organ yield from donors undergoing protocolized management of cardiac index, pulse pressure variation and mean arterial pressure driven by invasive hemodynamic monitoring to donor managed according to the current standard practice of no intervention.

The preceding overview of recent and current donor intervention portfolio clearly reflects efforts that extend preexisting concepts rather than explore novel approaches. The nature of these efforts contrasts starkly with the rich tapestry of mechanisms for possible therapeutic intervention that have emerged from animal models. Examples of mechanistic approaches that have been investigated in animals but have not percolated up to human investigation include:

Table 1: Donor intervention studies listed in clinicaltrials.gov*

ClinicalTrials.gov number	Start date	End date (projected)	Study title	Study status	Enrollment (projected)	Study design
NCT00245830	10/03	UNK	Ischemic Preconditioning of Liver in Deceased Donors	Completed	100	Treatment, Randomized, Single Blind, Active Control, Parallel Assignment, Efficacy Study
NCT00115115	3/04	12/07	Donor Dopamine and Initial Graft Function	Completed	487	Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study
NCT00260676	9/04	(9/09)	Protective Ventilatory Strategy in Organ Donors	Recruiting	200	Treatment, Randomized, Open Label, Active Control, Parallel Group Assignment, Safety/Efficacy Study
NCT00238030	12/04	UNK	Thyroxine Replacement in Organ Donors	Recruiting	30	Treatment, Randomized, Double-Blind, Placebo Control, Single Group Assignment, Efficacy Study
NCT00998972	9/06	(1/10)	N-acetyl-cysteine (NAC) and Kidney Graft Function	Recruiting	236	Treatment, Randomized, Single Blind (Subject), Uncontrolled, Parallel Assignment, Efficacy Study
NCT00718575	8/08	(7/11)	The Effects of Glucose / Ischemic Preconditioning on Reperfusion Injury in Deceased Donor Liver Transplantation	Recruiting	(100)	Treatment, Randomized, Single Blind (Subject), Parallel Assignment, Safety/Efficacy Study
NCT00975702	4/09	(6/12)	Remote Ischemic Preconditioning in Abdominal Organ Transplantation (RIPCOT)	Enrolling by Invitation	580	Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator), Active Control, Parallel Assignment, Safety/Efficacy Study
NCT00987714	8/09	(2/11)	Monitoring Organ Donors to Increase Transplantation Results (MOnITeR)	Recruiting	(960)	Randomized, Open Label, Uncontrolled, Parallel Assignment

*Search terms: Brain death; Donor AND management AND transplant; Donor AND ischemia; Donor AND procurement; Donor AND preservation; Donor AND reperfusion; Organ AND ischemia; Organ AND procurement; Organ AND preservation; Organ AND reperfusion; Preservation AND injury; Preservation AND ischemia; Preservation AND reperfusion; Transplant AND injury; Transplant AND ischemia; Transplant AND reperfusion.

- Inhibition of apoptosis through induction or overexpression of anti-apoptosis survival genes such as Bcl-2, Bcl-xL and A20
- Prevention of leukocyte adhesion through blockade of intercellular adhesion molecule-1 (ICAM-1), P-selectins and E-selectins
- Induction of cytoprotective genes such as heme-oxygenase-1 (HO-1), an integral component of the endogenous self-defense system that maintains cellular homeostasis
- Administration or induction of carbon monoxide (CO), a gaseous regulatory and cytoprotective molecule that protects vascular endothelial cells, controls vasomotor tone, inhibits the coagulation cascade, down-regulates pro-inflammatory cytokines and inhibits apoptosis.
- Inhibition of complement activation by transfer of a complement regulatory molecule
- Amelioration of microcirculatory damage through administration or transfer of an antagonist against endothelin or platelet activating factor antagonist or by enhancing the local synthesis of nitric oxide by transfer of inducible nitric oxide synthethase (iNOS)

Unfortunately, none of these innovative approaches that target molecular pathways have been tested in the humans.

Principles of Organ Preservation

After the ischemia and injury sustained during the tumultuous process of brain or cardiac death, organs are first procured and then preserved prior to transplantation. The general principles of organ preservation – static cold storage in a special solution – that were developed many decades ago are still, quite remarkably, operational today. University of Wisconsin (UW) solution, developed in the 1980s, remains the gold standard preservation fluid to this day. However, as it is a colloid solution characterized by high viscosity, high potassium content and requirement for additives and filtration, there has been recent renewed interest in histidine tryptophan ketoglutarate (HTK), a solution developed in a crystalloid perfusate developed in 1970s. Initial enthusiasm based on reports that HTK achieved comparable outcomes at lower cost compared to UW for kidney, liver and pancreas transplantation have, more recently, been countered by contradictory reports suggesting inferior outcomes (18–21).

Recent Trials in Organ Preservation

A search of the literature and the www.clinicaltrials.gov website has shown that innovation in organ preservation, like innovation in donor intervention, has had a narrow excursion from standard practice (Table 2) (22–24). Two additives to standard preservation solution have recently been tested in human clinical trials. The pan-caspase inhibitor, IDN-6556, has been assessed as an additive to the liver perfusate and preservation solution, with or without intravenous administration to the recipient during the first 24 h after liver reperfusion (NCT00080236; Table 2). Peak aminotransferases and the number of apopototic cells were significantly reduced solely in the group that received organ treatment without recipient treatment (25). More recently, YSPSL, a recombinant antagonist of P-selectin, has been tested in several trials of kidney and liver transplantation. In addition to an intravenous dose administered prior to kidney or liver reperfusion, YSPSL was added to the solution for the final *ex vivo* flush (NCT00298168, NCT00450398 and NCT00876902; Table 2). No data from any of the YSPSL trials have been published.

In addition to additives, new preservation solutions are also under investigation. Polysol, a low viscosity solution containing 21 amino acids, vitamins and other nutrients to improve mitochondrial function and energy, has been tested in rodent liver and intestinal as well as porcine kidney transplant models (26). IGL-1 is a novel solution that contains a biopolymer, polyethylene glycol, to provide not only colloidal support but also immunoprotection by creating steric hindrance that blocks allorecognition (27). Results of the first multi-center, randomized trial of IGL-1 in kidney transplantation showed improvement in early posttransplant kidney function with lower median serum creatinine levels from days 6 to 14 and a more rapid creatinine drop between days 4 to 15 (28). Another concept that has driven discovery of new preservations solutions is to increase oxygen availability during static storage. Perfluorocarbons (PFCs) are hydrocarbons where the hydrogen atoms have been replaced by fluorine atoms that dissolve and release high amounts of oxygen. Oxygenated PFC has been used with UW solution in the 'two-layer' method of pancreas preservation prior to islet isolation (NCT00592280; Table 2) (29). A dynamic approach to increasing oxygen availability has been 'persufflation', direct perfusion of gas through an organ's vasculature. Retrograde venous delivery of humidified oxygen has been tested predominantly in animal models of kidney and liver transplantation, although recently, the group in Essen, Germany, has reported a pilot trial of persufflation supplementing static cold storage for a small number deceased donor livers showing increased tissue ATP concentrations and improved early aerobic metabolism (30).

Although static preservation remains the standard practice for all solid organs, there has been a recrudescence of interest in machine perfusion. Perfusion was a technique developed four decades ago that disappeared when preservation solutions improved enough to allow for static storage. Perfusion results in continuous circulation of energy substrates and washout of waste products, for organ rehabilitation and recovery, and for assessment of tissue metabolism and viability through measurement of preservation fluid parameters. Currently, hypothermic machine preservation for kidneys has gained popularity, particularly for organs from suboptimal donors at increased risk of delayed graft function. A recent international randomized controlled trial randomly assigned one kidney to machine perfusion and the other to cold storage for 336 consecutive deceased donors (31). Hypothermic machine perfusion achieved a lower risk of delayed graft function (adjusted OR 0.57; $p = 0.01$) and a lower risk of graft failure (HR 0.52, $p = 0.03$) translating into improved 1-year graft survival (94% vs. 90%; $p = 0.04$) compared to cold static storage. On the heels of this emerging data, a comprehensive cost effectiveness analysis of pulsatile versus static preservation was undertaken by the Health Technology Assessment program of the National Institute for Health Research in the United Kingdom (32). Unfortunately, conclusions were limited by insufficient data of adequate quality. In the arena of liver transplantation, the first human clinical trial of hypothermic machine perfusion has just been reported (33). Twenty livers procured from brain dead donors less than 65 years of age with less than 25% macrovesicular steatosis were subjected to between 3 and 7 h of hypothermic machine preservation with Vasosol® solution supplemented with anti-oxidants, metabolic substrates and vasodilators after an initial period of cold static storage in UW solution.

Table 2: Organ preservation studies listed in clinicaltrials.gov*

ClinicalTrials.gov number	Start	End (projected)	Organ	Study title	Study status	N	Study design
NCT00284726	12/00	UNK	Lung	The Effect of Cold Storage Solutions on Ischemic Injury in Lung Transplantation	Ongoing; Not recruiting	UNK	UNSPECIFIED
NCT00737880	7/01	1/04	Pancreas	Histidine-Tryptophan-Ketoglutarate (HTK) vs. University of Wisconsin (UW) Perfusion in Clinical Pancreas Transplantation	Completed	68	Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Safety Study
NCT00151593	2/02	UNK	Liver	Evaluation of Celsior® in Liver Transplant Preservation	Completed	140	Treatment, Non-Randomized, Open Label, Historical Control, Single Group Assignment, Safety/Efficacy Study
NCT00080236	11/03	UNK	Liver	Safety and Efficacy Study of a Caspase Inhibitor in Patients Undergoing Liver Transplantation	Ongoing; Not Recruiting	100	Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study
NCT00225472	6/04	7/07	Kidney	Organ Preservation Media Investigation	Completed	20	Non-randomized, Open Label, Active Control, Single Group Assignment,
NCT00879268	7/04	2/08		Vasosol Organ Perfusion Solution and Medtronic Portable Bypass System	Completed	20	Non-randomized, Open Label, Historical Control, Single Group Assignment, Safety/Efficacy Study
NCT00298168	5/06	9/07	Kidney	YSPSL for Prevention of Delayed Graft Function Part B	Completed	60	Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Safety/Efficacy Study
NCT00450398	3/07	12/07	Liver	YSPSL for Prevention of Delayed Graft Function in Deceased Donor Liver Transplantation	Ongoing; Not Recruiting	12	Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Safety/Efficacy Study
NCT00994981	9/07	9/08	Living Donor Liver	Magnesium Administration in Liver Transplantation and Reperfusion Injury	Completed	61	Prevention, Randomized, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Placebo Control, Parallel Assignment, Efficacy Study
NCT00592280	10/07	(8/10)	Pancreas	Two-Layer Method Preservation and Resuscitation of the Deceased Donor Pancreas Before Transplantation	Enrolling by Invitation	34	Prevention, Open Label, Historical Control, Single Group Assignment, Safety Study
NCT00876902	5/08	3/09	Liver	YSPSL for Prevention of Ischemic Reperfusion Injury in Patients Undergoing Deceased Donor Liver Transplantation	Ongoing; Not Recruiting	36	Prevention, Randomized, Double Blind (Subject, Investigator), Placebo Control, Parallel Assignment, Safety/Efficacy Study

*Search terms: Brain death; Donor AND management AND transplant; Donor AND ischemia; Donor AND procurement; Donor AND preservation; Donor AND reperfusion; Organ AND ischemia; Organ AND procurement; Organ AND preservation; Organ AND reperfusion; Preservation AND injury; Preservation AND ischemia; Preservation AND reperfusion; Transplant AND injury; Transplant AND ischemia; Transplant AND reperfusion.

Compared to transplants using livers UW solution matched for donor and recipient age, Model for End-Stage Liver Disease score, and cold and warm ischemia times, transplants using machine-perfused exhibited a trend toward less early allograft dysfunction (5% vs. 25%; $p = 0.08$) and significantly shorter transplant hospitalization length of stay (10.9 ± 4.7 vs. 15.3 ± 4.9 days; $p = 0.006$). There were no differences in rates of primary non-function (none in either group), vascular or biliary complications, graft survival or patient survival.

Perhaps the most novel and exciting preservation approach under investigation is the use of normothermic perfusion as it represents the greatest departure from standard practice (34). Normothermia offers the advantages of allowing restoration of normal aerobic metabolism and energy balance along with clearance of anaerobic metabolites, essentially providing a platform for organ assessment, repair, resuscitation and treatment using pharmacologic agents and/or viral vectors for gene delivery. Disadvantages of normothermic perfusion center on considerable logistic challenges. The process must be integrated with the basics of organ procurement: the donor operation, initial preservation, transport to the transplant center and finally implantation into the recipient. Typically, organs are procured and immediately placed into cold static storage enabling simple transport to the transplant center. Normothermic perfusion must then be established at the transplant center. The set-up is complex, likely to be different for different organs, and requires highly trained personnel. Furthermore, the organ must be continuously monitored until the time of transplantation. Considering the high logistical hurdles, normothermic perfusion must yield strong benefits before its acceptance and adoption.

Normothermic perfusion has been investigated for several organs. In the realm of kidney and liver preservation, investigation remains in animal models without convincing evidence of benefit. However, for lung preservation, normothermic perfusion has successfully negotiated preclinical animal models and is currently the basis of a ground-breaking clinical trial (35,36). Lungs are procured in a standard fashion, transported from the donor hospital to the transplant center under standard conditions of cold storage and then placed in an *ex vivo* perfusion chamber. The lungs are then perfused with an asanguinous solution maintained at normal pH, pCO_2, electrolyte composition and glucose concentrations beginning at room temperature with gradual escalation up to 37°C. Mechanical ventilation in a protective mode with inspired oxygen concentration of 21% is initiated when 32°C is attained. At the end of the normothermic perfusion period, the lungs are cooled, taken off the circuit and returned to static hypothermic storage until transplantation. The investigators have demonstrated that this technique preserved alveolar barrier integrity and diminished histologic markers of ischemia/reperfusion injury including cellular edema, interstitial hemorrhage and leukocyte infiltration.

Barriers to Innovation in Donor Management and Organ Preservation

The derivative portfolio of clinical trials involving donor intervention and organ preservation that I have presented strongly suggests that unique and substantial barriers hinder progress in this critically important investigative area. There are conceivably an infinite number of actual and potential stakeholders when considering trials involving deceased donors themselves or their organs. The stakeholder list begins with the principal investigator(s) who initiates the effort by approaching the OPO staff and medical board. Ultimately, donor intervention proposals percolate through OPO channels to a large number of abdominal and thoracic transplant physicians for consideration. If scientifically and clinically embraced by all of these parties, proposals must then be presented to donor hospital physicians, nurses, administration and institutional review boards along with donor families. It is worth remembering that donors are not concentrated in a few hospitals but rather scattered throughout the community. Therefore, a primary barrier to innovation is the need to reach consensus across a broad coalition of parties that stem from distinctive spheres.

A second obstacle is the logistics of individual and institutional informed consent for the donor and the potential organ recipients. The ethics and appropriate regulation of research on deceased donors have been discussed (37,38). The definition of human subjects on which federal policy is based clearly does not encompass deceased donors. In spite of the lack of a federal mandate, the prevailing institutional practice is to ensure oversight, most frequently through the mechanism of an institutional review board. Similarly, although deceased donors are legally dead, informed consent for research from the family is typically secured. It is unarguable that the circumstances are tragic and provide a difficult backdrop to explain the planned research and thereby secure consent. Nevertheless, to respect and protect the deceased, to minimize the family's emotional distress, and to maintain public trust in the medical profession, consent from the donor family is expected and standard.

On the recipient side, potential recipients of organs involving either donor management or organ preservation should ideally be informed of and provide consent within the context of an institutionally approved protocol for any clinical trial. The problem is particularly vexing for trials that expose donors to a novel agent or treatment. Although some organs are indeed placed early in the donation process, many organs are placed much later and often even after organ procurement. Therefore, some or all recipients remain unknown until well into the donor management period or even after organ procurement. Moreover, even when organs are placed early, unexpected circumstances can and frequently arise that necessitate alternative placement. The imperative for institutional review board

approval and individual recipient consent represent substantial logistical obstacles to donor intervention and organ preservation trials.

Within the context of institutional oversight and individual consent, a very provocative question is whether donor intervention should be contingent on unanimous acceptance by designated recipients. While this may be ideal, there are reasons to suggest that this will be impractical. From a scientific perspective, the intervention may need to be delivered early in the process and or for a specific period of time for optimal effect. Awaiting organ placement and/or consent on the part of multiple potential recipients, even if possible, would introduce delay that may be not only undesirable but also detrimental. The necessity for institutional oversight would demand emergency consideration and approval by institutional review boards. Irrespective of whether recipient consent precedes or follows donor or organ treatment, there is substantial concern for undue coercion. Pressure comes from the fact that refusal to consent is tantamount to declining that specific opportunity for transplantation. Pressure is also exerted by the compressed timeline and stress inherent to transplantation. The setting is poorly suited for an unhurried and thorough discussion of the rationale, risks and potential benefits of an experimental approach to donor management or to organ preservation with either the individual or the institutional review board.

A third major obstacle lies in trial design with regard to safety and efficacy. If a systemic intervention is administered to the donor, even if it is intended to improve the function of just one organ, its impact on all other organs will need to be considered and assessed. More importantly, though, is the lack of established endpoints for trials intended to improve early graft function. The classic targets of patient and/or graft survival are too coarse and insufficiently discriminating for interventions designed to attenuate ischemia/reperfusion injury. For the kidney, the incidence of delayed graft function, most often defined as the need for hemodialysis within a week of transplantation, is the leading candidate for donor intervention and organ preservation trials. While it may indeed be 'the best we have', it is widely recognized that the indications and thresholds for dialysis differ substantially according to patient, physician and transplant center. The subjectiveness of this critical decision calls into question its validity as an objective assessment of early kidney allograft function. In the liver arena, ischemia/reperfusion trials uniformly compare liver tests such as aminotransferases and bilirubin between study groups at specified time points after transplantation. Although a study might show statistically significant differences in laboratory parameters, criticisms often center on the lack of a meaningful clinical outcome difference. These two examples illustrate the challenge with regard to endpoint selection for donor intervention and organ preservation trials that must be uniquely solved for each organ.

Conclusion

In summary, I would argue that there are currently substantial scientific, logistical and ethical obstacles that discourage innovation in donor management and organ preservation. Unfortunately, the pathway to executing such studies is obscure, lacking clear tread marks and obvious guideposts. The issues that obstruct investigation are fundamental and unique to the transplant setting; relevant precedents are unavailable. These issues extend well beyond the reasonable reach of individual investigators and require a larger body to first define and then tackle. The transplant community must demand leadership and vision from professional organizations and governmental agencies to set the research agenda, to give it the highest priority, and, most importantly, to dedicate the necessary resources to ensure a vigorous engagement of the community. Research to improve donor and organ quality is an absolute imperative as it offers the greatest promise to relieve suffering and prolong the lives of our patients.

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